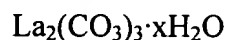


--10. A method to treat hyperphosphataemia in a subject which method comprises administering to said subject an amount of lanthanum carbonate of the formula



wherein x has a value from 3 to 6
effective to treat said hyperphosphataemia.

11. The method of claim 10 wherein x has a value from 3.5 to 5.

12. The method of claim 11 wherein x has a value from 3.8 to 4.5.

13. The method of any of claims 10-12 wherein said administering is by an oral route.--

REMARKS

The claims have been amended to conform to U.S. practice, obviate the rejection under 35 USC 101, and more particularly point out the invention. New claims 10-13 are supported on page 3, beginning at line 20 and throughout the specification. No new matter has been added and entry of the amendment is respectfully requested.

The Invention

The invention resides in the unexpected discovery that lanthanum carbonates with waters of crystallization or hydration between 3 and 6 moles of water per mole of lanthanum carbonate are particularly effective in absorbing phosphate both *in vivo* and *in vitro*. This ability finds practical use in treating patients whose phosphate levels in the blood are too high. Rapid binding is extremely important because the drug is generally administered with food and must bind phosphate in the food before the phosphate is absorbed into the bloodstream. Further, the binding must take place at acidic conditions associated with the stomach. The rapid binding at very low levels of the lanthanum carbonate hydrates of the invention permit acceptable dosage levels and patient acceptance. Accordingly, the claims are directed to methods of treating

hyperphosphataemia using the phosphate hydrates of the invention and pharmaceutical compositions for administering these hydrates. Nothing in the cited art suggests the use of lanthanum carbonate with waters of hydration in the range of 3-6 in this manner.

The Rejections

The rejections of claims 5, 6 and 9 on formal grounds are believed obviated. Due to the cancellation of claim 4, claim 5 no longer depends on a multiple dependent claim. Claims 6 and 9 have been canceled. Claim 6 has been replaced by new claim 10 which is in U.S. format and recites a positive step. Accordingly, these bases for rejection can be withdrawn.

Further, claim 9 was rejected as anticipated by several documents. Claim 9 has been canceled.

The remaining rejections are under 35 USC 103.

All claims, claim 1-9 were rejected as obvious over Junji (JP 62/145024).

Applicants assume that the evaluation by the Office of Junji is based on the abstract which indicates that carbonates or inorganic acid compounds of rare earth elements such as Y, La, Ce, Pr, etc. are used as immobilizing agents for phosphate ions. The abstract suggests that such compounds would be useful in treating hyperphosphataemia. However, the abstract also indicates that the immobilizing agents immobilize and remove phosphate well only at pH levels above 6. Clearly, this is disadvantageous as the pH conditions in the stomach are much lower.

Further, as the Office points out, Junji merely discloses a large genus of salts, of which the claimed hydrate is only a single subspecies. It has been held at least twice by the Federal Circuit that disclosure of a genus of this type does not render unpatentable an undisclosed species. For example, in *In re Baird*, 16 F.3d 380, 29 USPQ2d 1550 (Fed. Cir. 1994), claims to copolymers formed from a specific diol and a list of three specific dicarboxylic acids were held patentable over a genus which included these species. In *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941, 1944 (Fed. Cir. 1992), a particular ammonium salt of the herbicide dicamba was held patentable over the disclosure of a genus which included this salt. Copies of these decisions are attached for the convenience of the Office.

While there may be a certain logic to the Examiner's reasoning that it would have been obvious to pick any arbitrary species of the genus taught by Junji and have expected it to work,

this is not the position taken by the Federal Circuit. And clearly, there is no expectation that these species would work dramatically better than the remaining members of the genus.

Further, the Office has pointed to no description in Junji of the method of preparation of the desired hydrates set forth in claims 7 and 8. There appears to be no cited document which describes this method of preparation.

Here, there is no specific disclosure of $\text{La}_2(\text{CO}_3)_3 \cdot x\text{H}_2\text{O}$ where x has a value from 3-6 in the Junji document. While generically included in the abstract, this specific species is clearly not suggested. Thus, there is not even a *prima facie* case that these specific compounds are obvious.

Further, the specification supporting these claims demonstrates that these species show unexpected results. For example, Figure 1 shows the percent phosphate removal at 5 minutes obtained when lanthanum carbonate at various levels of hydration is used in the experiment set forth on page 6 of the specification. In this *in vitro* experiment, a solution at pH 3, close to the pH level found in the digestive tract was used. Sample 1 has water of hydration such that $x=8.8$. Sample 2 is the unhydrated form. Sample 3 contains 4.4 waters of hydration. Clearly sample 3 is far superior. More detailed data are seen in Table 1 on page 7 which show that after only two minutes sample 6, which has 3.8 waters of hydration, has already removed 88.1% of the phosphate from solution whereas sample 2 has removed only 28.1%.

These unexpectedly excellent results for lanthanum carbonate in the claimed range of hydration clearly support patentability of methods to treat hyperphosphataemia with these compounds. And the specification at page 12 demonstrates that *in vivo*, the hydrated form is successfully excreted and does not pass into the circulation system.

The Examiner states that the determination of dosage having the optimum therapeutic index is within ordinary skill. It is assumed that this is intended to address the further limitations of claim 5. Claim 5 is patentable for the same reasons set forth above; however, the enhanced efficiency of the claimed lanthanum carbonate hydrates permits these lower dosages.

The remaining bases for rejection are based individually on Yanagihara, Mineely and Mzareulishvili. These documents teach individually the lanthanum carbonate hydrates wherein x is 5, 3 and 6 respectively. The Office takes the view that because these specific compounds may be diluted in water, water represents a pharmaceutical excipient and places these within the scope of the claims. It is respectfully submitted that this is an error of law. These documents are

strictly directed to the chemistry of the hydrates *per se* and make no suggestion that the hydrates be formulated for administration to individuals, or even that they be added to water.

None of the cited documents suggests combining lanthanum carbonate hydrate with water. In Yanagihara the pentahydrate is precipitated from aqueous solution, not combined with water as a carrier. In Mineely the reaction of the trihydrate with molten $K_2S_2O_7$ was studied. Water is not mentioned. In Mzareulishvili the reaction of lanthanum nitrate with various carbonates was studied and found to yield the hexahydrate. There is no suggestion that any of the products be combined with water.

Thus, it cannot fairly be said that the Yanagihara, Mineely, or Mzareulishvili documents suggest pharmaceutical compositions of these species.

Conclusion

The cited art fails to suggest the claimed methods of the invention which utilize lanthanum carbonate hydrates having waters of hydration in the particular range 3-6 which are particularly effective at absorbing phosphate at low pH. Nothing in the cited art points to these specific species for this use. Further, the claimed species are unexpectedly superior to other lanthanum carbonate hydrates. Accordingly, it is believed that claims 1-3, 5, 7, 8 and 10-13 are in a position for allowance and passage of these claims to issue is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 391442000200. However,

the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

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